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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/332,866	06/15/99	LEVEUGLE B	A52026US

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1642	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)	
09/332,866		
Examiner	**Group Art Unit**	
M. T. DAVIS	1642	

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 04/12/00.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 2, 12-21, 24, 25, 27. is/are pending in the application.

Of the above claim(s)_____ is/are withdrawn from consideration.

☐ Claim(s)_____ is/are allowed.

☒ Claim(s) 2, 12-21, 24, 25, 27 is/are rejected.

☐ Claim(s)_____ is/are objected to.

☐ Claim(s)_____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on_____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on_____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)_____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:_____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 12

☐ Interview Summary, PTO-413

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other_____

Office Action Summary

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

Applicant's election of group II, claims 2, 12-21, 24-25, and 27 in Paper No. 9 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Accordingly, claims 2, 12-21, 24-25, and 27 are examined.

PRIORITY DATE

The Examiner has established a priority date (06/15/99) for the instantly claimed application serial number 09/332866 as the application 60/089281 to which priority is claimed is not available. Applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

OBJECTION

1. Claims 14 and 19 are objected to because claims 14 and 19 contain a period (.) in the claims.

2. Claim 12 is objected to because it is a substantial duplicate of claim 2.

Applicant is advised that should claim 2 be found allowable, claim 12 will be rejected under 35 U.S.C. 101 as being a substantial duplicate thereof, When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to reject the other as being a substantial duplicate of the allowed claim. See MPEP 706.03(k).

SEQUENCE RULES

1. Claims 24, 25 do not need to comply with sequence rules because the amino acids are not recited in claims 24 and 25.

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821-25 for the following reasons: The amino acid sequences recited on page 21 of the specification are not accompanied by sequence identification numbers.

DEPOSIT REQUIREMENT

The specification is objected to under 35 USC 112, first paragraph, as failing to provide an enabling disclosure and failing to provide an adequate description of the claimed invention without evidence that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials.

A deposit of the hybridoma cell lines which has ATCC Accession No:12526 is required to enable the invention of claims 14 and 19. Because it is not clear that cell lines possessing the identical structure and functional properties of those which has ATCC Accession No:12526 are known and publicly available or can be reproducibly isolated without undue experimentation, a suitable deposit for patent purposes is required. Without a publicly available deposit of the above cell lines, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of the claimed cell lines which produce chemically and functionally distinct antibodies is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequence to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementary determining regions, can be folded to form similar binding contours, which result in similar immunochemical characteristics (Fundamental Immunology, 242, William E. Paul, ed. 3rd ed. 1993). The claimed cell lines are distinct and unique cell lines which produce specific antibodies, having unique properties, one of ordinary skill in the art would be forced into undue experimentation in order to make the claimed cell lines in view of the lack of exemplary materials and in view of the unpredictability associated with obtaining the exact species repeatedly. A

deposit of the claimed cell lines would satisfy the requirements of 35 USC 112 first paragraph in this case. See CFR 1.801-CFR 1.809.

In addition, the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803-1.809 for additional explaination of these requirements.

Claims 14 and 19 are rejected under USC 112, first paragraph, for the reasons set forth in the objection to the specification.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH

Claims 19, 24 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 19 is indefinite, because claim 19 is incomplete. The claim does not recite a step of administering the claimed binding agent, which is neccessary for performing the claimed method.

2. Claims 24 and 25 are indefinite, because one of ordinary skill in the art could not determine which amino acids comprises the claimed amino acids number 135 to 150. Although the prostate specific antigen (PSA) is known in the art, the number of the starting amino acid in the recited PSA sequence could vary, depending whether the recited sequence contain a signal sequence or not. For example, under MPSRCH sequence homology search, the claimed sequence of SEQ ID NO:1, from amino acid number 139 to 163 corresponds to the amino acid sequence

from amino acid number 163 to 187 in the prostate specific antigen sequence taught by Lundwall et al, 1987, FEBS Lett, 214: 317-322.

3. Claims 24 and 25 are indefinite for the use of the language "amino acid sequences 135 to 150", because 135 and 150 are amino acid numbers.

4. Claims 2, 12-21, 24-25, 27 are indefinite, because claim 2 does not recite a step correlating administration step to the preamble of the claim.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Claims 2, 12-21, 24-25, and 27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

1. Claims 2, 12-16, 19-21, 24-25, and 27 are drawn to a method for treating prostate cancer comprising administering a binding agent, wherein said binding agent binds to circulating prostate specific antigen. More specifically said binding agent binds to an epitope of prostate specific antigen (PSA) comprising SEQ ID NO:1, or amino acid sequences 135 to 150 of PSA, or has ATCC Accession No: 12526. Claims 17-18 are drawn to a method of inducing an immune response or increasing the immunogenecity of an antigen, comprising administering a binding agent, wherein said binding agent binds to an epitope of circulating prostate specific antigen. Claims 16, 17, 18 are further drawn to said method for treating prostate cancer or said method of

inducing an immune response or increasing the immunogenecity of an antigen, wherein the binding agent forms an immunogenic complex with the antigen.

The specification discloses antibody AR47.47 which specifically binds to the epitope of amino acids 139-163 (SEQ ID NO:1) of PSA. The specification discloses that a binding agent could also bind to amino acids 135 to 150.

The specification discloses, in example 7 and figure 9, injection of a commercially available anti-PSA antibody RLSD09 (p.25) four times into Balb/c mice. A tumor cell line1-PSA is injected into said mice between the third and fourth antibody injection. The specification speculates that the tumor burden in treated mice is considerably lower than that of the control mice, and that there is a negative correlation between the level of Ab3, the antiidiotypic antibody against PSA, produced as a result of anti-PSA antibody injection, and the number of tumor loci.

The specification discloses an example (Example 11) of 1) treating mice first with antibody AR 47.47, which binds specifically to SEQ ID NO:1, wherein the antibody is linked to the immunogenic carrier KLH, then 2) inoculating the mice with PSA-transfected tumor cells, and 3) continuing administration of the claimed antibody after tumor inoculation. The specification further discloses that injection of said antibody produces idiotypic antibody Ab2 and anti-idiotypic antibody Ab3. The specification also dicloses that out of three experiments using Balb/c mice, in one experiment, #7, treated mice have reduced lung tumor foci, as compared to the control groups. In addition, the specification discloses that out of three experiments using DBA mice, in two experiments, # 6 and 9, treated mice have 73% and 100%, respectively, of mice without

tumor, as compared to the control groups, having 44% and 60%, respectively, of mice without tumor. The control mice of experiment # 12 have 80% of mice without tumor as compared to the treated mice of experiment # 12, having 60% of mice without tumor.

The specification discloses another example (Example 12) of first inoculating mice with PSA-transfected tumor cells, and then administer to said mice antibody AR 47.47. The specification also discloses that no therapeutic effect was observed on tumor progression.

The results in the specification however are questionable. In figure 9, the data from injection of anti-PSA antibody RLSD09 is highly variable. Yet there is no statistical analysis presented in figure 9. Furthermore, it is not clear what the intention of figure 9 is for. If the intention is to demonstrate a correlation between the level of Ab3 and the number of tumor loci, it seems that there is no clear correlation between the level of Ab3 and the number of tumor loci, because in the control mice injected with PBS, the level of Ab3 is the same, whereas the number of tumor loci increases.

In addition, it is unpredictable that injection of antibody AR 47.47 would significantly reduce prostate tumor growth. In example 11, for treating Balb/c mice, only one out of three experiments shows treated mice with decreased tumor loci as compared to control mice, and for treating DBA mice, two out of three experiments show an increased percentage of mice without tumor. There is no statistical data to compare the significance level between experiments. It is not even clear how many mice are used in each experiment. It is questionable whether said reduction of tumor loci or inhibition of tumor growth in mice is significant. Furthemore, even if the claimed

data is statistically significant, it is questionable whether the mice model could be applied to human, because the results are highly variable even just within different types of mice. In other words, the results are unpredictable when antibody AR 47.47 is injected into human patients with prostate cancer. Moreover, even Applicant admits that the claimed tumor model would not reflect what is happening in human because prostate cancer is considered to be a slow progressing disease, whereas the growth rate of the tumor in example 11 is much faster (p.39). Furthermore, in example 11, the tumor cells are injected after antibody treatment. This example could not be applied to treament human with prostate cancer, because the specification does not disclose how to predict which individuals would develop prostate cancer, nor exactly when said individuals would have prostate cancer to administer the claimed antibody before prostate cancer is detected. If the claimed antibody is only administered after prostate cancer has been detected, then said treatment is not effective, as shown in example 12.

It is unpredictable that injection of antibody that binds specifically to amino acids 135 to 150 would significantly reduce prostate tumor growth, in view of the above unpredictability of a method of treating prostate cancer, comprising administrating an antibody that binds to amino acids 139 to 163, and in view of the fact that the region 135 to 150 overlaps with the region 139 to 163, further in view of the fact that neither applicant, nor the art have shown by exemplification that antibody that binds specifically to amino acids 135 to 150 would significantly reduce prostate tumor growth.

Furthermore, it is unpredictable that administration of the claimed antibody AR 47.47 would produce an anti-idiotypic antibody Ab3 which recognizes the claimed epitope consisting of SEQ ID NO:1. The specification discloses that the presence of Ab3 could only be found when a tested plate is coated with PSA, i.e. detecting the binding of Ab3 and PSA, whereas an assay using the claimed PSA peptide of SEQ ID NO:1 to coat the plate has not been standardized at the time of filing the instant application, because in many cases the positive control performed with the antibody AR47.47 shows negative signal (p.31). In other words, it is possible that the Ab3 detected by Applicant is an antibody that binds to an epitope different from SEQ ID NO:1.

The above mentioned reasons for the unpredictability of treating prostate cancer, or inducing an immune response, or increasing the immunogenecity of an antigen, apply as well to a complex of the claimed binding agent and its antigen.

The specification provides insufficient guidance with regard to the issues raised above and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

In the event that Applicant could overcome the above 112, first paragraph rejection, claims 2, 12-13, 15-21, 24-25, 27 are still rejected under 112, first paragraph, scope.

Claims 2, 12-13, 15-21, 24-25, 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating prostate cancer comprising administering antibody AR47.47 which specifically binds to the epitope of amino acids 139-163 (SEQ ID NO:1) of PSA, does not reasonably provide enablement for a method of treating prostate cancer comprising administering 1) a binding agent that binds to circulating PSA or to the epitope of amino acids 139-163 (SEQ ID NO:1) of PSA, or to amino acid sequences 135 to 150, or 2) complex of said binding agent and its antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 2, 12-13, 15-21, 24-25, 27 are drawn to a method of treating prostate cancer comprising administering a binding agent that binds to circulating PSA or to the epitope of amino acids 139-163 (SEQ ID NO:1) of PSA, or to amino acid sequences 135 to 150 of PSA. Claims 17-18 are drawn to a method of inducing an immune response or increasing the immunogenecity of an antigen, comprising administering a binding agent, wherein said binding agent binds to an epitope of circulating prostate specific antigen. Claims 16, 17, 18 are further drawn to said method for treating prostate cancer or said method of inducing an immune response or increasing the immunogenecity of an antigen, wherein the binding agent forms an immunogenic complex with the antigen.

The specification discloses a method fo treating prostate cancer comprising administering antibody AR47.47 which specificcally binds to the epitope of amino acids 139-163 (SEQ ID

NO:1) of PSA. The claims however encompass a method of treating prostate cancer comprising administering any compound, including chemical compounds, that specifically binds to circulating PSA or to the epitope of amino acids 139-163 (SEQ ID NO:1) of PSA, or to amino acid sequences 135 to 150.

It is unpredictable that prostate cancer could be treated by administration of any compound, including chemical compounds, that binds to circulating PSA or to the epitope of amino acids 139-163 (SEQ ID NO:1) of PSA, or to amino acid sequences 135 to 150 of PSA. It is well known in the art PSA is an enzyme found in elevated levels in the circulation system in patients with prostate cancer. However the role of PSA in prostate cancer is not known. It is not clear how administration of any compound, for example a label that is specifically bound to amino acids 139-163, but not to other region of PSA, would successfully treat prostate cancer, because there is no correlation between administration of a labeled amino acids 139-163 and reduction of prostate tumor growth. In addition, the specification does not teach how to make any compound that binds to circulating PSA or to the epitope of amino acids 139-163 (SEQ ID NO:1) of PSA, or to amino acid sequences 135 to 150 of PSA; and one of skill in the art could not correlate from one example of treating cancer by administering antibodies that bind to circulating PSA or to the epitope of amino acids 139-163 (SEQ ID NO:1) of PSA to treating cancer by administering any compound that binds to circulating PSA or to the epitope of amino acids 139-163 (SEQ ID NO:1) of PSA, or to amino acid sequences 135 to 150 of PSA. In the absence of a method of how to make any compounds that binds to circulating PSA or to the epitope of amino acids 139-

163 (SEQ ID NO:1) of PSA, or to amino acid sequences 135 to 150 of PSA, it would be undue experimentation for one of skill in the art to make any compounds that binds to circulating PSA or to the epitope of amino acids 139-163 (SEQ ID NO:1) of PSA, or to amino acid sequences 135 to 150 of PSA, and to use said compounds for treating prostate cancer.

In view of the above absence of a method of teaching of how to make any compound that binds to circulating PSA or to SEQ ID NO:1, or to amino acid sequences 135 to 150 of PSA, it would be equally undue experimentation for one of skill in the art to make a complex of the claimed compounds, and to use said complex for treating prostate cancer or inducing an immune response or increasing the immunogenecity of an antigen.

The specification provides insufficient guidance with regard to the issues raised above and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention as broadly as claimed.

REJECTION UNDER 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 2, 12, 13, 15-19, 24-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Giri, Dipak Kumar, 1995, EP 0 652 014.

Claims 2, 12, 13, 15-19, 24-25 are drawn to a method for treating prostate cancer comprising administering a binding agent, wherein said binding agent specifically binds to circulating prostate specific antigen. More specifically said binding agent binds to an epitope of prostate specific antigen (PSA) comprising SEQ ID NO:1, or amino acid sequences 135 to 150 of PSA. Claims 17-18 are drawn to a method of inducing an immune response or increasing the immunogenecity of an antigen, comprising administering a binding agent, wherein said binding agent binds to an epitope of circulating prostate specific antigen. The language "comprising" reads on any amino acid sequence of any length, including full length PSA, provided it contains SEQ ID NO:1, or amino acid sequences 135 to 150 of PSA.

Giri, Dipak Kumar teach a method for arresting growth of both prostastic hypertrophy and prostastic carcinoma in human, by administrating antibodies specifically reactive against human PSA (Example 4).

Thus the method taught by Giri, Dipak Kumar is the same as the claimed method of claims 2, 12, 13, 15-16, 19, 24-25. Furthermore, the method taught by Giri, Dipak Kumar is the same as the claimed method of claims 17-18, because the method of the prior art comprises the same method steps as claimed in the instant invention, that is, administering an antibody that binds to an epitope of circulating prostate specific antigen. Thus the claimed method is anticipated because

the method will inherently lead to inducing an immune response or an increase in immunogenecity of an antigen. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

REJECTION UNDER 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 12, 13, 20-21 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Giri, Dipak Kumar, 1995, EP 0 652 014, in view of Mazuwa, N et al, 1993, Neuroscience Res, 18(1): 27-34.

Claims 2, 12, 13, 20-21 and 27 are drawn to a method for treating prostate cancer comprising administering a binding agent, wherein said binding agent specifically binds to circulating prostate specific antigen and induces a therapeutic immune response and wherein said binding agent is conjugated to an immunogenic carrier, keyhole limpet hemocyanin (LKH).

The teaching of Giri, Dipak Kumar has been set forth.

Mazuwa, N et al teach conjugation of an antibody to KLH for making anti-idiotypic antibodies.

Therefore, it would have been obvious to one of ordinary skill of the art at the time the invention was made to conjugate the antibody taught by Giri, Dipak Kumar with KLH, using the method taught by Mazuwa, N et al, and then to administer said conjugated antibody to a patient with prostate cancer, because administration of antibodies conjugated to KLH would produce anti-idiotypic antibodies, as taught by Mazuwa et al, and because it is well known in the art that anti-idiotypic antibodies could be used for treating cancer. One of ordinary skill in the art would have been motivated to treat prostate cancer comprising administering an antibody, wherein said antibody specifically binds to circulating prostate specific antigen, and wherein said antibody is

conjugated to an immunogenic carrier, keyhole limpet hemocyanin (LKH), with a reasonable expectation of success.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Tam B. Davis whose telephone number is (703) 305-2008. The examiner can normally be reached on Monday-Friday from 9:30am to 3:30pm, except on Wesnesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4227.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0916.

Minh-Tam B. Davis

August 16, 2000

SUSAN UNGAR, PH.D
PRIMARY EXAMINER